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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,730	04/24/2001	Se-Jin Lee	JHU1470-3	6537

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/841,730	Lee, S.-J. et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 29, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above, claim(s) *6-12, 15-19, and 21-39* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 13, 14, 20, and 40-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 17, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *10/12*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed April 24, 2001, is a continuation in part of 09/626,896, filed July 7, 2000, which is a continuation in part of 09/485,046, filed May 5, 2000, which a national stage filing of PCT/US98/15598, filed July 28, 1998, which claims benefit to US provisional application 60/054,461, filed August 1, 1997.

Claims 1-42 are pending and currently under examination.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-5, 13, 14, 20 and 40-42, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that while Applicants submit that the groups I, II and III are independent and patentably distinct, a search of the claims for group I would reveal art which would be relevant to groups II and III (see Applicants' election bottom of page 1). This is not found persuasive because first, as noted by Applicants, each of the groups are drawn to independent and patentably distinct inventions. Second, while the embodiment for the use of various variants of the activin II receptor encompassed by each of the three groups may be similar, the search for each of the distinct inventions encompassed by the groups is not co-extensive. More specifically, a complete search of the relevant art for the embodiments encompassed by group I would not provide a complete search of the embodiments encompassed by the inventions of Groups II or III. For a proper restriction MPEP 808.02 states that 'the Examiner, in order to establish reasons for insisting upon restriction, must show by appropriate

explanation of one of the following: (A) Separate classification, (B) Separate status in the art when classifiable together, or (C) a different field of search. In the instant case, Applicants arguments are not persuasive because each of the groups set forth in the restriction requirement have a different classification and require a different search of the relevant art.

The requirement is still deemed proper and is therefore made **FINAL**.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

RMS 2/10/03

Claims 1-42 are pending. Claims 6-12, 15-19 and 21-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9. Claims 1-5, 13, 14, 20 and 40-42, drawn to a transgenic non-human mammal comprising a transgene encoding a truncated Activin Type II receptor, are currently under examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The second application must be an application

for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). Additionally, Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the claims under examination of this application.

Specifically, CIP applications 09/626,896, 09/485,046, and provisional application 60/054,461 fail to provide literal or figurative support for the use of activin receptors in the construction of non human transgenic animals. In particular, only GDF/myostatin, one member of a large TGF-β superfamily of receptors, is described in any detail in each of the co-pending applications. Therefore, because activin type II receptors are only first presented in the present application, the priority accorded the instant application is the filing date of this application, April 24, 2001.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. For example, on page 13, lines 5, 11-13 and 18 and page 15, line 11 multiple hyperlinks to databases and search/comparison programs are recited. Applicant

is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Objections

Claims 1-5, 13, 14, 20 and 40-42 are objected to because of the following informalities:

Applicants have elected group I, claims 1-5, 13, 14, 20 and 40-42, as it is drawn to a transgenic non-human mammal comprising a transgene encoding a truncated Activin Type II receptor. Presently, the claims are broader than the elected invention reading on the non-elected inventions of transgenic bird (group II) and transgenic fish (group III). The claims should be amended to encompass the elected invention. Claim 20 is dependent on non-elected claims 6 and 11 and recites expression of non-elected inventions of myostatin or follistatin. Claims 40-42 recite the expression of the transgenes of myostatin or follistatin which are directed to non-elected inventions.

Additionally, claim 1 appears to have a typographical error where it recites 'corresponding' twice in the final line of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 13, 14, 20 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a nucleic acid sequence which encodes a truncated Activin receptor IIB, wherein said truncated Activin receptor is a murine truncated receptor consisting of amino acid residues 1-174, operatively linked to the myosin light chain promoter and 1/3 enhancer, wherein elevated expression levels of the Activin Type II B receptor result in an increased muscle mass as compared to a corresponding nontransgenic animal and methods of making said transgenic mouse, does not reasonably provide enablement for making or providing all transgenic non human animals nor other truncated Activin Type II receptors whose expression levels are regulated by other promoters encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are broad as they are drawn to providing and making any non human transgenic animal, and use of a transgene comprising any truncated form of the Activin Type II receptor and any promoter for expression of said transgene. The specification provides a working example for a single transgenic mouse comprising a single transgene construct of a truncated murine Activin receptor IIB, whose expression is regulated by the myosin light chain promoter and 1/3 enhancer. The specification demonstrates that this particular transgene construct when inserted into the genome of a mouse by conventional methods of transgenics results in elevated expression levels of the Activin Type II B receptor and an increased muscle mass is said transgenic mice. With respect to the breadth outside the single working example of a truncated Activin receptor the instant invention is prophetic relying on the teachings of the art for generating the claimed transgenic animals and methods of making and using. Given the unpredictability of the art of transgenics, the specification fails to provide a nexus by providing

the necessary guidance to overcome the art recognized obstacles of generating transgenic animals.

First, the specification fails to provide the necessary teachings or guidance with regard to the generation of any animal, other than a transgenic mouse. The art of transgenics is not a predictable art with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species. This observation is specifically supported by Hammer *et al*. who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Ebert *et al*. report a transgenic pig that did not develop an expected phenotype of growth during the rapid growth phase, when transfected with a Moloney murine leukemia virus rat somatotropin fusion gene (p. 277, summarized in abstract). The observation is further supported by Mullins *et al*. who report on transgenesis in the rat and larger mammals. Mullins *et al*. state that "a given construct may react very differently from one species to another" (see Summary section). Wall *et al*. further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 62, first paragraph). The observations of Mullins *et al*. and Wall *et al*. are more specifically supported within the TGF-β super family as exemplified by altered expression of myostatin. Myostatin, like Activin, is a member of the TGF-β super family

whose expression has been associated with muscle development and mass. McPherron *et al.* (PNAS, 1997) teach that 'Unlike in mice, a myostatin null mutation in cattle causes an reduction in sizes in internal organs and only a modest increase in muscle mass' (page 12460, bottom of first column). As noted in the specification (page 132, paragraph 358) and in the art of record while a role for Activin in muscle development has been implicated because of the complexity of regulation of muscle development the specific mechanism and role of the Activin is not presently known. Given such species differences in the expression of various transgenes, in particular the TGF-β super family members, one of skill in the art would have been required to undergo undue experimentation to determine which promoters and specific transgene constructs would produce the desired phenotype in all non-human animals. In the instant case, the specific elements used in the construction of the DNA plasmids for use in generating the transgenic animals were not discovered by Applicant, rather they were derived from the art based on reports of their function in mice. Absent of evidence to the contrary, it is not clear that these elements would be functional in other animal species in the same manner as they have been demonstrated in mice. Further, given that other related members of the TGF-β super family result in different phenotypes in mice and cattle, there is no expectation that the phenotype observed for the transgenic mouse disclosed in the instant specification would extend to other non human animals.

As a second issue, while the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animals comprising a transgene of interest, it is not

predictable if the transgene would be function at a level and specificity sufficient to cause a particular or specific phenotype. The art of transgenics is not a predictable art with respect to transgene behavior or resulting phenotype. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species and to the transgene used. This observation is specifically supported by Hammer *et* al. who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Similarly, Ebert *et al.* report a transgenic pig that did not develop an expected phenotype of growth during the rapid growth phase, when transfected. Further, as noted above, McPherron *et al.* teach that expression of mutant forms of other TGF-β super family members result in phenotypic differences among the species examined (page 12460). Additionally, the role of the Activin receptor *in vivo* is still a subject of active research and defining its specific role has been complicated by a redundancy in the TGF-β super family. For example, in the pancreas Yamaoka *et al.* (1998) teach that the Activin receptor may be dispensable for normal development of islet cells (page 300, top of first column). However, while a redundancy may make a particular member of a the TGF-β super family dispensable in some cases, this does not simply extend to all types of alterations in the TGF-β super family or particular phenotypes produced by said alterations. For example, Yamaoka *et al.* (1998) teach that two alterations of TGF-β which should result in a null

phenotype, over-expression of a TGF-β dominant negative mutant and a TGF-β knockout construct, result in different affects on acinar cells in the pancreas (page 300, middle of first column). Thus, in view of the art even the expression of two different mutant transgenes from the TGF-β superfamily which should result in the same affect result in different phenotypes *in vivo* when expressed as transgenes.

As a third issue, the claims as written reads on use of promoters defined first functionally as muscle specific and more specifically as directed to the myosin light chain promoter/enhancer, however, the specification fails to provide the necessary guidance with regard to a promoter other than myosin light chain promoter and 1/3 enhancer specifically disclosed in the instant specification for use in mice. The art of transgenics is not a predictable art with respect to promoters and expression vectors. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the specific promoter/gene combination(s). The specific promoter used and the specific cDNA used could be important in determining the resulting phenotype. Wall generally supports the observation by stating that "our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." (see page 61, last paragraph). While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animals comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. Mathew *et al.* (US Patent 5,885,794) teach this to be particularly important in the expression of

Activin receptor IIB. Mathew *et al.* teach the isolation and characterization of the Activin receptor II. In the characterization of the affect of Activin receptor in Xenopus embryos Mathew *et al.* teach that the phenotype observed is sensitive to the amount of expression of the Activin receptor provided. Importantly, the level of expression correlated with a decrease in muscle actin expression (column 19, lines 42-56). Therefore, the art teaches that the level of expression of Activin Receptor II is critical in generating a particular phenotype. Thus, the level and the specificity of expression of a transgene as well as the phenotype of a transgenic animal produced are greatly dependent on the specific transgene construct used. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct are all important factors in controlling the expression of the transgene. In the instant case, because the art teaches that the phenotypic affect of the Activin receptor II is dose dependent, the specification fails to describe any other promoter besides the myosin light chain promoter and 1/3 enhancer which will provide the necessary levels of expression which will result in increase muscle mass as required by the claims.

As discussed above, the claims are broad, encompassing any non-human transgenic animal containing the DNA constructs set forth in the claims. The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In view of the quantity of experimentation necessary to determine the parameters listed above, the lack of

direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the production of transgenic animal models of any species, or other promoters which broadly meet the functional language encompassed by the claims, and the general unpredictable state of the art with respect to the generation of transgenic animals of all species, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claim is confusing in the recitation of 'whereby the progeny are hatched' because non-human mammals, such as porcine and bovine recited in the claims, are not hatched, they are born. Additionally, the claim is incomplete as it directed to culturing the embryo because *in vitro* conditions for culturing an non-human mammal embryo would not result in progeny. The claim appears to be drafted as it was directed to producing birds.

Amending the claim to reflect language of claims 40 or 41 for maturing an embryo or implanting an embryo would obviate the basis of the rejection.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 41 recites the limitation "the animal" in line three. There is insufficient antecedent basis for this limitation in the claim. The preamble of the claim refers to 'animal food products', not any specific animal. Amending the claim to recite 'an animal' would obviate the basis of the rejection.

Conclusion

No claim is allowed. The claims are free of the art of record because the art fails to teach or make obvious a transgenic non human animal expressing a truncated Activin Type II receptor wherein said non human animal exhibits increased muscle mass. In particular, due to the unpredictability of transgene behavior and evidence that the activin receptor is involved in various organs and tissues (for example FSH regulation Crowley *et al*. US Patent 5,658,876) one would not have simply predicted that expression of Activin Type II receptor mutants would result in increased muscle mass. The claims are free of the art of record, however the claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

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